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Mutations in a TGF-β Ligand, *TGFB3*, Cause Syndromic Aortic Aneurysms and Dissections

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ABSTRACT

BACKGROUND Aneurysms affecting the aorta are a common condition associated with high mortality as a result of aortic dissection or rupture. Investigations of the pathogenic mechanisms involved in syndromic types of thoracic aortic aneurysms, such as Marfan and Loeys-Dietz syndromes, have revealed an important contribution of disturbed transforming growth factor (TGF)-β signaling.

OBJECTIVES This study sought to discover a novel gene causing syndromic aortic aneurysms in order to unravel the underlying pathogenesis.

METHODS We combined genome-wide linkage analysis, exome sequencing, and candidate gene Sanger sequencing in a total of 470 index cases with thoracic aortic aneurysms. Extensive cardiological examination, including physical examination, electrocardiography, and transthoracic echocardiography was performed. In adults, imaging of the entire aorta using computed tomography or magnetic resonance imaging was done.

RESULTS Here, we report on 43 patients from 11 families with syndromic presentations of aortic aneurysms caused by *TGFB3* mutations. We demonstrate that *TGFB3* mutations are associated with significant cardiovascular involvement, including thoracic/abdominal aortic aneurysm and dissection, and mitral valve disease. Other systemic features overlap clinically with Loeys-Dietz, Shprintzen-Goldberg, and Marfan syndromes, including cleft palate, bifid uvula, skeletal overgrowth, cervical spine instability and clubfoot deformity. In line with previous observations in aortic wall tissues of patients with mutations in effectors of TGF-β signaling (*TGFBR1/2, SMAD3,* and *TGFB2*), we confirm a paradoxical up-regulation of both canonical and noncanonical TGF-β signaling in association with up-regulation of the expression of TGF-β ligands.

CONCLUSIONS Our findings emphasize the broad clinical variability associated with *TGFB3* mutations and highlight the importance of early recognition of the disease because of high cardiovascular risk. (J Am Coll Cardiol 2015;65:1324–36) © 2015 by the American College of Cardiology Foundation. Open access under CC BY-NC-ND license

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The transforming growth factor (TGF)-β pathway plays an important role in many medically relevant processes, including immunologic maturity, inflammation, cancer, and fibrosis, as well as skeletal, vascular, and hematopoietic homeostasis (1). With the discovery of dysregulated TGF-β signaling in *Fbn1* knockout mice, the TGF-β pathway was revealed as a key player in the pathogenesis of thoracic aortic aneurysm development in Marfan syndrome (MFS; [Mendelian Inheritance in Man (MIM) 154700]) (2,3). MFS is a multisystemic disease characterized by cardiovascular, ocular, and skeletal features caused by mutations in the *FBN1* gene (4). More recently, we and others identified pathogenic mutations in the genes encoding the TGF-β receptor (TGFBR) subunits TGFBR1 and TGFBR2 (5,6), the signaling transducer SMAD3 (7), the ligand TGFB2 (8,9), and the inhibitor SKI (10), occurring predominantly in patients with syndromic presentations of thoracic aortic aneurysms and dissections (TAAD), designated Loeys-Dietz syndrome (LDS1 [MIM 609192] [11]; LDS2 [MIM 610168] [11]; LDS3 [MIM 613795] [also known as aneurysms-osteoarthritis syndrome] [7,12,13], LDS4 [MIM 614816] [8]), and Shprintzen-Goldberg syndrome (SGS [MIM 82212]) (13,14). The finding of human mutations in a ligand, receptors, a signaling transducer, and an inhibitor of the TGF-β pathway confirms the essential role of TGF-β signaling in aortic aneurysm development.

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Recently, de novo mutations in the gene encoding the TGFB3 ligand (*TGFB3*) were reported in 2 girls exhibiting a syndrome affecting body growth (either short or tall stature) accompanied by skeletal features reminiscent of MFS or LDS, but without significant vascular involvement (15–17). Here, we report that *TGFB3* mutations cause a syndromic form of aortic aneurysms and dissections, characterized by cardiovascular, craniofacial, cutaneous, and skeletal anomalies that significantly overlap with other TGF-β vasculopathies, particularly those within the LDS clinical spectrum.

ABBREVIATIONS AND ACRONYMS

LAP = latency-associated peptide

LDS = Loeys-Dietz syndrome

LOF = loss of function

MFS = Marfan syndrome

MIM = Mendelian Inheritance in Man

SNP = single nucleotide polymorphism

TAAD = thoracic aortic aneurysms and dissections

TGF = transforming growth factor

TGFBR = transforming growth factor beta receptor

METHODS

PATIENTS. All patients or relatives provided written informed consent for participation in this study and, if applicable, publication of photographs. Family 1

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